APPENDICES

APPENDIX A

[LOGO]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

December 28, 1990

Philip R. Tracy
President and Chief Executive Officer
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Mr. Tracy:

As you are aware, the laboratory evaluation and clinical development of AZT as a treatment for HIV infection was the result of a highly successful collaboration among investigators at your company, the National Cancer Institute (NCI) and other institutions. During the course of this collaboration, Burroughs Wellcome filed related patent applications world-wide, and several U.S. patents already have issued that claim AZT-based pharmacautical compositions, as well as the use of AZT to treat AIDS and ARC and to increase the T-lymphocyte count of patients infected with HIV. For the reasons discussed below, we believe that NCI investigators should have been named as coinventors on these patents and request your cooperation in correcting inventorship.

AZT was developed and evaluated by Dr. Jerome Horwitz in 1964, and tested against murine retroviruses in the 1970's. We understand from public statements made by officials of Burroughs Wellcome that its testing of AZT in late 1984 also was limited to non-human animal retroviruses. As Dr. David Barry of Burroughs Wellcome indicated in his letter of March 30, 1987, to Dr. Bruce

Chabner of NCI, activity against such viruses is not considered to be predictive of activity against HIV. Several prior art references cited by the Examiner in the prosecution of Burroughs Wellcome's patents disclose the same tests that apparently were conducted by your company in late 1984. We note that Burroughs Wellcome's patents might be challenged under U.S. patent law if the concept of clinical efficacy against HIV could be extrapolated from studies in non-human test systems.

We understand that in February 1985, when Burroughs Wellcome provided "Compound S" (AZT) to NCI for evaluation, AZT's efficacy against live HIV had not been shown and that investigators at Duke had tried and failed to demonstrate anti-HIV activity. As a matter of patent law, the development of the assay by NCI and its use to test the activity of AZT against HIV at NCI was required to form a "conception" prior to the filing date of Burroughs Wellcome's first relevant British patent application on March 16, 1985. NCI staff also made numerous other contributions to the design and execution of the research collaboration. Thus, NCI investigators should have been named as coinventors on this and subsequent patent applications. The clinical testing in which NCI participated was required to establish a legally sufficient conception at least for some of the patent claims, particularly those directed to increasing T-cell counts.

Our assertion of inventorship rights on behalf of the Department of Health and Human Services is consistent with Federal patent law and is the culmination of a thorough review that was prompted by the Department's more active protection and management of its intellectual property interests following enactment of the Federal Technology Transfer Act of 1986. In reaching our conclusion on inventorship, we carefully reviewed our records of the underlying research collaboration, the various public statements and Congressional testimony of officials of Burroughs Wellcome, and the prosecution histories of the

relevant U. S. patents. We also conducted a detailed analysis of this case, including consultation with outside patent counsel.

We are prepared to discuss the specific facts of this collaboration, as well as the law of inventorship, and we invite Burroughs Wellcome to provide additional facts or legal analysis that you regard as relevant. Mr. Reid G. Adler, Director of the NIH Office of Technology Transfer (301-496-0750), will be pleased to coordinate arrangements for a meeting if you would find that helpful. We fully acknowledge your company's efforts in bringing AZT to market as an AIDS therapeutic and look forward to resolving this matter of inventorship in the near future.

Sincerly yours,

/s/ William F. Raub
WILLIAM F. RAUB, PHD.
Acting Director

cc: Reid G. Adler, J.D.

APPENDIX B

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NORTH CAROLINA
NEW BERN DIVISION

No.: 91-41-CIV-4-H

BURROUGHS WELLCOME CO.,
Plaintiff,

VS.

BARR LABORATORIES, INC.,
Defendant.

No.: 92-134-CIV-4-H

BURROUGHS WELLCOME CO.,
Plaintiff,

VS.

NOVOPHARM, INC.,
Defendant.

AND RELATED CROSS-ACTION.

DEPOSITION OF ALEXANDRA M. LEVINE
Los Angeles, California
April 20, 1993

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* * * *

[27] Q. When you were first contacted by Barr Laboratories' attorneys, were you told that obviousness was an issue in this case?

A. No.

Q. Do you understand what I mean by "obviousness"?

A. No.

Q. That the use of AZT as a treatment for HIV infection was obvious to one skilled in the art—well, withdraw that.

That anybody reviewing the prior literature on AZT would have known that AZT would work as a treatment for HIV infection?

A. Yes. We discussed that.

Q. And what was discussed in that regard?

A. The conversation related to questioning me whether or not I believed as a clinician that there was enough information available with the data on various animal retroviruses to indicate that the same kind of activity might be possible * * *

* * * *

[29] Q. And what did he explain to you in that regard?

A. He explained that in my understanding, the patent law requires that a substance be newly—stop for a minute.

To be patentable, an idea or a product must have a valid basis for believing that it might work in a given circumstance or illness. It has to be something creative in that regard with data to suggest that there was reason to believe, there was reasonable evidence to believe that the new invention or new idea would be active in the disease discussed or system discussed.

Q. Do you have any patents, Dr. Levine?

A. No, I don't.

Q. Have you ever filed any patent applications?

A. No, I haven't.

* * * *

[41] Q. Dr. Levine, what opinions do you intend to render at trial?

A. I intend to state in my opinion, that activity of a given antiretroviral compound, and in this case AZT, in mouse cells using a mouse retrovirus or other animal retroviruses in animal cells would not reasonably be expected to indicate similar activity in human cells or in human retroviral disease.

Q. What is the basis of that opinion, Dr. Levine?

A. The basis of opinion relates to an understanding that human immunodeficiency virus is unique in itself and different from other retroviruses, and that by studying an animal cell and an animal virus, there would be no reasonable belief that that could be directly correlated to a different virus and a different living system.

Q. You are not a retrovirologist, are you, Doctor?

[42] A. I am not.

Q. And you have no expertise in retrovirology?

A. Correct.

Q. But you are going to testify as to the differences between various retroviruses, is that what you are telling me?

A. No. I am going to testify that using a model, for example, of development of cancer drugs, which was the model that I am most familiar with which has been time honored and tested over many decades, it has been clearly demonstrated and shown that in order to determine activity of a given compound in a human, one must, in fact, look at human illness in human lines or in human tumors.

Q. For many years in a cancer context compounds were tested against murine cancers; isn't that correct, Dr. Levine?

A. Yes, it is.

* * * *

[55] Q. —two different pharmaceutical formulations, do you believe that you could have given this to a pharmacist or pharmacologist back in February of 1985 and had the AZT that somebody had previously made to you made into a phamaceutical formulation?

A. Yes. Based on some information later in the document, I believe I could give this to a pharmacologist to make in different formulations.

Q. Okay. And turning to the second page of the draft patent application on the third page of this exhibit document, Bates No. BR083175.

A. Yes.

Q. And refering you to the fourth paragraph down, could you have following the instructions in the fourth paragraph taken this pharmaceutical formulation of AZT and given it to a patient?

A. I most certainly could have, but I would not have. This is way too broad. It includes tremendously high doses and doses that would be [56] very uncomfortable for me. I would not think it appropriate to use this piece of paper to administer, for example, 250 milligrams per kilogram body weight per day.

Q. Well, focusing, Dr. Levine, on the physician's preferable range of 5 to 40 milligrams per kilogram body weight per day, could you, if you wanted to—let's assume for the purposes of this question that you want to administer this pharmaceutical formulation of AZT to a patient.

A. That's a difficult question in the way it is worded. Certainly I could. I could do anything in the world, but I would not automatically use even in the preferred dose 40 milligrams per kilogram body weight per day. I would not do that.

Q. I am not asking you what you would do. I am asking could you follow the directions in this paragraph and administer a pharmaceutical formulation of AZT to a patient following the most preferable dose range of 5 to 40 [57] milligrams, the instructions as to subdosage and the directions as to unit dosage form in the most preferable range of 100 to 400 milligrams of active ingredient per unit dosage form?

A. I could if I had been allowed to do so via an agreement or a statement from the Human Research Committee or the Institutional Review Board.

Q. And if you had chemists make you up some AZT, a pharmacist put that AZT in a chemical formulation and had dosed a patient per the instructions of this document, could you have then measured a patient with HIV infection, could you have then measured whether or not there was a beneficial effect on that patient as a result of administering this compound?

A. I could so determine.

Q. And if you had done all these things, had it made, put in pharmaceutical formulation, given it to a patient with HIV infection, again, using the most preferable range of dosing as laid out in this paragraph, would you have seen [58] a clinical benefit or therapeutic benefit at all? Not optimal therapeutic benefit but any therapeutic benefit?

MR. STUART: Objection as to form. The question is so incredibly broad.

BY MS. MEZEY:

Q. If you could answer the question, Dr. Levine, I would appreciate if you would do so.

A. It depends on the dose that was used. In some of the dosing here, I imagine that I would not have seen a benefit. In other of the dosing I might have seen a benefit.

Q. Okay. Focusing on the 5 to 40 milligrams per kilogram of body weight per day, would you have seen any therapeutic benefit administering 5 milligrams per kilogram of body weight per day?

A. Yes, I believe I would.

Q. And if you had administered 40 milligrams per kilogram of body weight per day, would you have seen some clinical benefit?

* * * *

[69] Q. They knew its half life?

A. Yes.

Q. They had done a whole body radiography of live animals?

A. Uh-huh. Yes.

Q. Now, Dr. Levine, if no HIV screen were available in late 1984 and early 1985, based upon all the information available to BW Co., would you have given this compound to human beings who were dying of HIV infection?

MR. STUART: Objection to form.

THE WITNESS: No, I would not.

BY MS. MEZEY:

Q. Were there any treatments available for HIV infection in late 1984, early 1985?

A. In late 1984 and 1985 there were several compounds that were being studied in human trials. One such compound was Suramin which had, for example, been tested in the human cell [70] system with human HIV prior to use in man, in clinical trials. So that your earlier question, in fact, wasn't the case in late 1984, early 1985. There had been established a human system with HIV.

Q. I understand that. But assuming that there were no such system, there were no treatments for HIV infection, you have all this information about AZT. You have spectacular nanomolar concentration of results in the murine retroviral assay, you have all of this other information, dosing, toxicity, live animal information about AZT, there is nothing out there to treat patients.

Would you have given this to your patients infected with HIV?

A. No. I would not, and I would not have been allowed to do so by the Human Research Committee without data in humans, some sort of human cells or systems that would have allowed them to believe that there was a reason to think there could be activity of that compound in [71] man.

There are many, many compounds that are being given by physicians in the community in desperation related to people who have AIDS. It is going on now, and it was definitely going on in 1984.

For example, the injections of murine into AIDS patients, the use of the Salk polio vaccine in AIDS patients.

There is an entire compendium of drugs or substances which have been used by individuals who believe that this is a desperate situation and, therefore, anything is doable or allowable.

And I don't believe that. I believe that in order to take a human being and experiment with that individual, you must have some valid scientific data to certainly suggest activity in human systems before going into man, have some evidence of activity.

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